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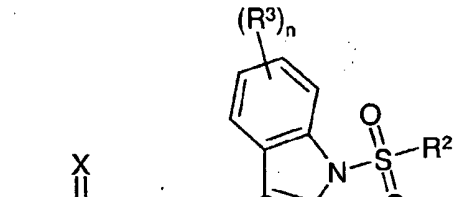
(54) Title: 1-SULFONYL SUBSTITUTED TRYPTOPHANE DERIVATIVES AND ITS USE AS INTEGRIN INHIBITORS



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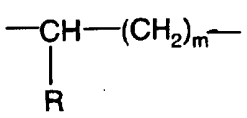
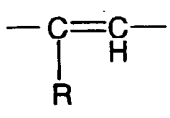


(a)



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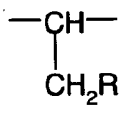

(c)

(57) Abstract: Trytophan derivatives of formula (1) are described: wherein Ar is an optionally substituted aromatic or heteroaromatic group; X is an oxygen or sulphur atom; Alk is a chain (a), (b) or (c), in which m is zero or the integer 1 or 2 and R is a carboxylic acid (-CO_2H) or a derivative or biostere thereof; R2 is an optionally substituted aliphatic group; R3 is an optional substituent; n is zero or the integer 1, 2 or 3; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of LFA-1 to its ligands and are of use in the prophylaxis and treatment of inflammatory diseases or disorders or autoimmune diseases.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

1-SULFONYL SUBSTITUTED TRYPTOPHANE DERIVATIVES AND ITS USE AS INTEGRIN INHIBITORS

This invention relates to a series of tryptophan derivatives and related compounds, to compositions containing them, to processes for their preparation and to their use in medicine.

A co-ordinated series of events beginning with vasodilation and increased vascular permeability together with exudation of fluid and plasma proteins results in inflammation. Simultaneously inflammatory cells infiltrate the site of inflammation, in response to inflammatory mediators generated at the site of initial lesion. Mediators that have chemotactic activity for leukocytes, the principle group of inflammatory cells, include chemokines such as IL-8, MCP-1, MIP-1 and RANTES, complement fragments and lipid mediators. By a process known as cell adhesion these circulating leukocytes localize at a precise point on the vascular endothelium, prior to crossing the endothelium to the site of inflammation.

Leukocytes are an important component of human peripheral blood that may be further divided into a number of different members. The leukocyte family consists of neutrophils, lymphocytes (B- and T-cell subtypes), monocytes, eosinophils and basophils. During an inflammatory response peripheral blood leukocytes are recruited to the site of inflammation or injury by a series of specific cellular interactions. A critical step in the inflammatory response is the adhesion of leukocytes to the vascular endothelium and migration from the circulation to the site of inflammation. The lymphocyte function associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18), which is present on the surface of all mature leukocytes except a subset of macrophages, has been identified as the major integrin that mediates lymphocyte adhesion and activation leading to a normal immune response as well as several pathologies (Springer, T. A., Nature, 1990, 346, 425-434). This cellular adhesion molecule belongs to the leukocyte-specific β_2 subfamily of integrins, in which a common β_2 subunit (CD18) is associated with distinct but

homologous α subunits. Other members of the family include Mac-1 ($\alpha_M\beta_2$, CD11b/CD18), p150.95 ($\alpha_X\beta_2$, CD11c/CD18) and $\alpha_D\beta_2$ (CD11d/CD18).

Amongst its many roles LFA-1 plays a key part in the adhesion to, and migration across vascular endothelium of leukocytes, particularly monocytes and neutrophils. The first step consists of leukocytes rolling along the vascular endothelium in the region of inflammation, mediated by sialyl Lewis^X on leukocytes interacting with E- and P-selectins expressed on the endothelium. This reversible interaction is followed by the stronger interactions of the second stage which are mediated by the interaction of leukocyte integrins (LFA-1 and Mac-1) with intracellular adhesion molecules (predominantly ICAM-1) which are induced on the endothelium in response to inflammatory mediators such as IL-1, LPS and TNF-α. A conformational change in LFA-1 and Mac-1 in response to chemokines such as IL-8, MIP-1-α, RANTES and lipid mediators results in a firm attachment of leukocytes to endothelium. A third stage in which LFA-1 and Mac-1 also play a role is the extravasation of the leukocytes between the cells forming the blood vessel walls which is followed by a final stage of leukocyte migration along concentration gradients of chemokines secreted by cells at the site of infection or inflammation. A further role for LFA-1 is a part (in combination with the major histocompatability protein, MHC on antigen presenting cells) in the interaction of T-cell receptor with antigen on antigen-presenting cells. On binding to an antigen presented on a MHC signalling through the T-cell receptor induces a conformational change in LFA-1 which greatly increases its affinity for its ligands (ICAM-1 and ICAM-2) on the antigen-presenting cell so stabilizing the interaction between antigen-specific T-cell and antigen-presenting cell.

The ligands for LFA-1 were identified by functional studies. These ligands (intercellular adhesion molecules) are known as ICAM–1 (Rothlein, R. et al, J. Immunol., 1986, 137, 1270-1274; Staunton, D. E. et al, Cell, 1988, 52, 925-933), ICAM-2 (Staunton, D. E. et al, Nature, 1989, 339, 61-64), ICAM–3 (Fawcett, J. et al, Nature, 1992, 360, 481-484; Vazeux, R. et al, Nature,

1992, 360, 485-488; De Fougerolles, A. R. and Springer, T. A., J Exp. Med., 1990, 175, 185-190), ICAM-4 (Bailly, P. et al.,Eur. J. Immunol., 1995, 25, 3316-3320) and ICAM-5 (Tian, L. et al, J. Immunol., 1997, 158, 928-936). ICAM-1, -2, –3, -4 and –5 are members of the immunoglobulin (Ig) superfamily and contain five, two and five Ig-like domains respectively of which the first domains are necessary and sufficient for interaction with LFA-1 (Binnerts, M. E. and van Kooyk, Y. Immunology Today, 1999, 20, 240-245). These ICAMs have distinct tissue distributions (Binnerts, M. E. *et al,* Eur. J. Immunol., 1994, 24, 2155-2160). For instance ICAM-1 is expressed on a variety of hematopoietic and non-hematopoietic cells including activated leukocytes, dermal fibroblasts and vascular endothelial cells (Dustin, M. L. et al, J. Immunol. 1986, 137, 245-254) and is upregulated at sites of inflammation by a variety of inflammatory mediators including LPS, IL-1 and TNF (Dustin, M. L. et al, J. Cell Biol. 1988, 107, 321-331).

Binding of LFA-1 to ICAMs mediates a range of lymphocyte functions including T-lymphocyte mediated target cell lysis, lymphokine production of helper T-cells in response to antigen presenting cells, immunoglobulin production through T-cell-B-cell interactions and natural killing of tumour cells. More specifically the LFA-1/ICAM-1 interaction is known to play a part in lymphocyte adhesion (Dustin, M. L. et al, J. Cell Biol. 1988, 107, 321-331), monocyte adhesion (Arnaout, M. A. et al, J. Cell Physiol. 1988, 137, 305-309) and polymorphonuclear leukocyte adhesion (Lo, S. K. et al, J. Immunol., 1989, 143, 3325-3329) to endothelial cells. Interactions of LFA-1 with ICAM-2 are thought to mediate natural killer cell activity (Helander, T. S. et al Nature, 1996, 382, 265-268) and interaction with ICAM-3 is believed to have a role in the initiation of the immune response (Simmons, D. L., Cancer Surveys, Cell Adhesion and Cancer, 1995, 24, 141-155).

Furthermore functional studies using monoclonal antibodies have demonstrated that members of the CD11/CD18 integrin family mediate a variety of cell-cell interactions including those that occur during inflammation (Springer, T. A. et al, Ann. Rev. Immunol., 1987, 5, 223-252). Thus

monoclonal antibodies to LFA-1 have been shown to inhibit T-cell activation (Dougherty, G. J. and Hogg, N. Eur. J. Immunol., 1987, 17, 943-47; Kuypers et al, Res. Immunol., 1989, 140, 461), conjugate formation required for antigen-specific cytotoxic T-lymphocyte mediated killing (Kishimoto T. K. et al, Adv. Immunol., 1989, 46, 149-182), natural killer (NK) cell killing (Krensky, A. M., et al, J. Immunol., 1983, 131, 611-616), the mixed lymphocyte response and T-cell dependent B-cell proliferation and differentiation (Davignon, D. et al, J. Immunol., 1981, 127, 590-595). Additionally such antibodies have been demonstrated to block T lymphoblast (Dustin, M. L. et al, J. Cell Biol., 1988, 107, 321-331) and neutrophil adhesion to endothelial cells (Smith, C. W. et al, J. Clin. Invest., 1989, 83, 2008-2017) including adhesion of T-cells to vascular endothelium (Hogg, N. and Landis, R. C., Curr. Opin. Immunol., 1993, 5, 383-390 and Picker, L. J. , Curr. Opin. Immunol., 1994, 6, 394-406). Antibodies blocking CD18 or ICAM-1 activity are the subject of for example International Patent Specifications Nos. WO93/02191, WO94/02175, WO94/12214, WO97/26912 and U.S. Patent No. 5,695,760.

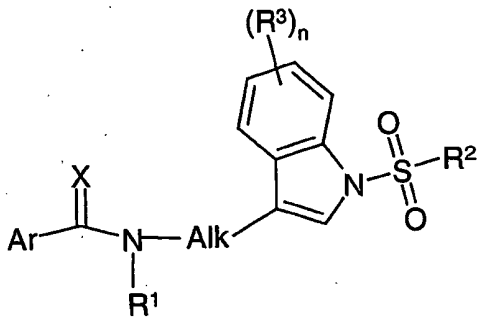
Following on from these observations that the LFA-1:ICAM-1 interaction is necessary for optimal T-cell function and the finding that anti-CD11a monoclonal antibodies (Mabs) can prolong graft survival in mice (Heagly et al, Transplantation, 1984, 37, 520-523) Mabs to CD11a have been tested for prevention of graft rejection in primates and humans. Thus *in vivo* administration of an anti-CD11a Mab prolonged skin allograft survival in cynomologous monkeys (Berlin, P. J. et al, Transplantation, 1992, 53, 840-849) and rat anti-murine CD11a antibody was effective in controlling steroid-resistant graft-versus-host disease in humans (Stoppa et al, Transplant. Int., 1991, 4, 3-7). Mabs are also efficacious in models of skin inflammation, e.g. models of contact hypersensitivity in mice (Scheynius, A. et al, J. Immunol, 1996, 156, 1804-1809). In humans, efficacy has been observed with anti-LFA-1 Mab in patients with psoriasis (Gottlieb, A. et al, J. Am. Acad. Dermatol., 2000, 42, 428-435).

It has further been demonstrated that antisense oligonucleotides to murine ICAM-1 can attenuate reperfusion injury and renal failure in rats (Stepkowski, S. M. et al, J. Immunol, 1994, 153, 5336-46; Haller et al, Kidney Int., 1996, 50, 473-480) and molecules of this type have been patented (for example U.S. Patents Nos. 5,591,623 and 5,580,969).

The use of biological molecules such as antibodies and oligonucleotides in treating inflammatory disease mediated by LFA-1 is not ideal since molecules of this type can suffer from lack of stability, low bioavailability, immunogenecity problems, high cost and possible risk of serious side effects. It is therefore preferable to use low molecular weight antagonists of the interaction between LFA-1 and its ligands since these molecules do not suffer from the same disadvantages as biological molecules. Hence such small molecules that block LFA-1 activity and so alter leukocyte trafficking are desirable as therapeutic agents for the treatment of chronic and acute inflammatory diseases or disorders and autoimmune diseases.

We have now found such a group of compounds which are potent inhibitors of the interaction between LFA-1 and ICAM-1. Such compounds are of use in medicine, for example in the prophylaxis and treatment of disorders involving inappropriate leukocyte trafficking and in acute and chronic inflammatory disorders as described herein.

Thus according to one aspect of the invention we provide a compound of formula (1)



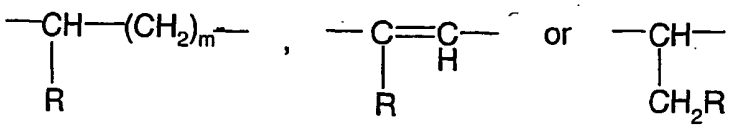
(1)

wherein:

Ar is an optionally substituted aromatic or heteroaromatic group;

X is an oxygen or sulphur atom;

Alk is a chain



in which m is zero or the integer 1or 2 and R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

R^2 is an optionally substituted aliphatic group;

R^3 is an atom or group $-L^1(Alk^1)_tL^2(R^4)_u$ in which L^1 and L^2 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^1 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^5$ [where R^5 is a hydrogen atom or an optionally substituted alkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-N(R^5)CO_2R^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $-N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom or an optionally substituted alkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^1 and L^2 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

n is zero or the integer 1, 2 or 3;

and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers) The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all

individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$)–enol (CH=CHOH) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

The compounds of formula (1) are potent and selective inhibitors of β2 integrins such as LFA-1. Members of the group are able to inhibit the action of LFA–1 at concentrations at which they generally have no or minimal action on β integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune and inflammatory disorders as described hereinafter.

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

Thus as used herein the term "alkyl", whether present as a group or part of a group includes straight or branched C_{1-10}alkyl groups, for example C_{1-6}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl groups and C_{3-10}cycloalkyl groups, for example C_{3-7}cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean straight or branched C_{2-10}alkenyl, C_{3-10}cycloalkenyl or C_{2-10}alkynyl groups such as C_{2-6}alkenyl, C_{3-7}cycloalkenyl or C_{2-6}alkynyl groups, for example $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCHCH_3$, -CCH, $-CH_2CCH$, $-CH_2CCCH_3$, cyclopentenyl or cyclohexenyl groups. Each of these groups may be optionally substituted on any carbon atom. Optional substituents that may be present include those optional substituents mentioned hereinafter in relation to optionally substituted aliphatic groups.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CH_2F$, and $-CH_2Cl$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-10}alkoxy for example C_{1-6}alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-10}alkylthio, e.g. C_{1-6}alkylthio such as methylthio or ethylthio groups.

The term "aliphatic group" is intended to include optionally substituted straight or branched C_{1-10}alkyl, e.g. C_{1-6}alkyl, C_{2-10}alkenyl e.g. C_{2-6}alkenyl or C_{2-10}alkynyl e.g. C_{2-6}alkynyl groups.

The term "heteroaliphatic group" is intended to include the optionally substituted aliphatic groups just described but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^3 where L^3 is a linker atom or group. Each L^3 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples of suitable L^3 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O), $-S(O)_2$-, $-N(R^8)$- [where R^8 is a hydrogen atom or an alkyl group], $-N(R^8)N(R^8)$-, $-N(R^8)O$-, $-CON(R^8)$-, $-OC(O)N(R^8)$-, $-CSN(R^8)$-, $-N(R^8)CO$-, $-N(R^8)C(O)O$-, $-N(R^8)CS$-, $-S(O)_2N(R^8)$-, $-N(R^8)S(O)_2$-, $-N(R^8)CON(R^8)$-, $-N(R^8)CSN(R^8)$-, or -

$N(R^8)SO_2N(R^8)$- groups. Where the linker group contains two R^8 substituents, these may be the same or different.

Particular examples of aliphatic groups include optionally substituted $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$, $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, or $-(CH_2)_2CCH$ groups. Where appropriate each of said groups may be optionally interrupted by one, two, three or more atoms and/or groups L^3 to form an optionally substituted heteroaliphatic group. Particular examples include optionally substituted $-L^3CH_3$, $-CH_2L^3CH_3$, $-L^3CH_2CH_3$, $-L^3CH_2CHCH_2$, $-L^3CH_2CCH$, $-CH_2L^3CH_2CH_3$, $-L^3CH_2L^3CH_3$, $-(CH_2)_2L^3CH_3$, $-L^3(CH_2)_2CH_3$ and $-(CH_2)_2L^3CH_2CH_3$ groups.

The optional substituents which may be present on aliphatic or heteroaliphatic groups include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, or alkoxy, haloalkoxy, hydroxy (-OH), thiol (-SH), alkylthio, amino ($-NH_2$), substituted amino, -CN, $-CO_2H$, $-CO_2R^9$ (where R^9 is an optionally substituted alkyl group), $-SO_3H$, $-SOR^9$, $-SO_2R^9$, $-SO_3R^9$, $-OCO_2R^9$, -C(O)H, $-C(O)R^9$, $-OC(O)R^9$, $-C(S)R^9$, $-C(O)N(R^{10})(R^{11})$ (where R^{10} and R^{11}, which may be the same or different is each a hydrogen atom or an optionally substituted alkyl group), $-OC(O)N(R^{10})(R^{11})$, $-N(R^{10})C(O)R^{11}$, $-CSN(R^{10})(R^{11})$, $-N(R^{10})C(S)(R^{11})$, $-SO_2N(R^{10})(R^{11})$, $-N(R^{10})SO_2R^{11}$, $-N(R^{10})C(O)N(R^{11})(R^{12})$ (where R^{12} is a hydrogen atom or an alkyl group), $-N(R^{10})C(S)N(R^{11})(R^{12})$ or $-N(R^{10})SO_2N(R^{11})(R^{12})$. Substituted amino groups include $-NHR^9$ and $-N(R^9)(R^{10})$ groups.

It will be understood that the terms optionally substituted aliphatic or heteroaliphatic chain include those optionally substituted aliphatic and heteroaliphatic groups just described where a terminal hydrogen atom is replaced by a covalent bond. Thus for example alkyl, alkenyl and alkynyl chains become alkylenyl, alkenylenyl and alkynylenyl chains respectively.

Particular non-limiting examples include a $-CH_2CH_3$ group becoming a $-CH_2CH_2-$ chain and a $-L^3(CH_2)_2CH_3$ group becoming a $-L^3(CH_2)_3-$ chain.

The term "aromatic group" is intended to include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12}aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups. Each of these aromatic groups may be optionally substituted by one, two, three or more R^{13} atoms or groups as defined below.

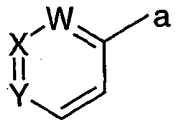
The term "heteroaromatic group" is intended to include for example optionally substituted C_{1-9}heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, benzotriazolyl, indolyl, indolinyl, isoindolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, qunoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl. Each of these heteroaromatic

groups may be optionally substituted by one, two, three or more R^{13} atoms or groups as defined below.

The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When Ar is an optionally substituted pyridyl group it may include any pyridyl group of formula (1a):



(1a)

where a represents the point of attachment to the rest of the molecule of formula (1), one of W, X and Y is a N atom and the other two are CH groups. When Ar is an optionally substituted phenyl group it may for example have the formula (1a) in which each of W, X and Y is a CH group. The hydrogen atom of any of the CH groups present in pyridyl or phenyl groups of formula (1a) may be optionally replaced by any R^{13} atom or group as described below.

Optional substituents which may be present on any carbon atom of the aromatic or heteroaromatic groups represented by Ar in compounds of formula (1) include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^2(R^{13a})_f$, where R^{13a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^2(R^{13a})_f$ group], $-CSR^{14}$, $-SO_3H$, $-SOR^{14}$, $-SO_2R^{14}$, $-SO_3R^{14}$, $-SO_2NH_2$, $-SO_2NHR^{14}$, $-SO_2N(R^{14})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON(R^{14})_2$, $-CSN(R^{14})_2$, $-N(R^{15})SO_2R^{14}$, [where R^{15} is a hydrogen atom or an optionally substituted alkyl group] $-N(SO_2R^{14})_2$, $-N(R^{15})SO_2NH_2$, $-N(R^{15})SO_2NHR^{14}$, $-N(R^{15})SO_2N(R^{14})_2$, $-N(R^{15})COR^{14}$, $-N(R^{15})CONH_2$, $-N(R^{15})CONHR^{14}$, -

$N(R^{15})CON(R^{14})_2$, $-N(R^{15})CSNH_2$, $-N(R^{15})CSNHR^{14}$, $-N(R^{15})CSN(R^{14})_2$, $-N(R^{15})CSR^{14}$, $-N(R^{15})C(O)OR^{14}$ or optionally substituted C_{6-12}aromatic or C_{1-9}heteroaromatic group; Alk^2 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_g-$ [where g is an integer 1 or 2] or $-N(R^{15})-$ groups; and f is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{14} or R^{15} groups are present in one of the above substituents, the R^{14} or R^{15} groups may be the same or different.

When in the group $-Alk^2(R^{13a})_f$ f is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in $-Alk^2$. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^2$. Clearly, when f is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^2 then Alk^2 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group $-NHR^{14}$ [where R^{14} is as defined above] or a group $-N(R^{14})_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

When R^{13a} is an optionally substituted C_{6-12}aromatic group it may be for example an optionally substituted phenyl group. When R^{13a} is an optionally substituted C_{1-9}heteroaromatic group it may be for example an optionally substituted furanyl, thienyl, pyrrolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl or pyrimidinyl group. Optional substituents that may be present on such aromatic or heteroaromatic groups include those R^{13} atoms and groups as just described.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^5$ wherein Alk^5 is a straight or branched optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C_{2-8}alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8}alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8}cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8}cycloalkylC_{1-8}alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8}heterocycloalkylC_{1-6}alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted C_{1-6}alkylthioC_{1-6}alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6}alkylsulfinylC_{1-6}alkyl group such as an methylsulfinylethyl group; an optionally substituted C_{1-6}alkylsulfonylC_{1-6}alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8}cycloalkyloxyC_{1-6}alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C_{3-8}cycloalkylthioC_{1-6}alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8}cycloalkylsulfinylC_{1-6}alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C_{3-8}cycloalkylsulfonylC_{1-6}alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkyl group such as an isopropoxycarbonyloxyethyl e.g a 1-(isopropoxycarbonyloxy)ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C_{3-}

$_{8}$cycloalkyloxycarbonyloxyC_{1-6}alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C_{1-8}alkylaminoC_{1-8}alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C_{6-12}aryl-N-C_{1-6}alkylaminoC_{1-6}alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C_{1-8}alkylcarbamoylC_{1-8}alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C_{6-10}arylC_{1-6}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-10}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-10}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C_{6-12}arylthioC_{1-8}alkyl group such as an optionally substituted phenylthioethyl group; a C_{6-12}arylsulfinylC_{1-8}alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C_{6-12}arylsulfonylC_{1-8}alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C_{4-8}imidoC_{1-8}alkyl group such as a succinimidomethyl or phthalamidoethyl group; a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C_{1-8}alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk^5 group include R^{13a} substituents described above.

It will be appreciated that in the forgoing list of Alk^5 groups the point of attachment to the remainder of the compound of formula (1) is via the last described part of the Alk^5 group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group would be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk^5 groups, where not specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined. Additionally these alkyl, alkenyl or alkynyl groups may optionally be interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L^3.

When Alk^2 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{15})-$ groups.

Particularly useful atoms or groups represented by R^{13} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkylamino e.g. aminoethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino e.g. hydroxyethylamino, imido, such as succinimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^5$ [where Alk^5 is as defined above], e.g. $-CO_2CH_3$ or $-CO_2CH_2CH_3$, C_{1-6}alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), $-SO_3R^{14}$, C_{1-}

$_{6}$alkylsulphinyl e.g. methylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylamino-sulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylamino-carbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylamino-carbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylamino-carbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonyl-amino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethyl-amino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonyl-amino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethyl-sulphonylamino or diethylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoyl-amino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino or C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the phenyl or pyridyl group represented by Ar.

In compounds of formula (1) derivatives of the carboxylic acid group R (-CO_2H) include carboxylic acid esters and amides. Particular esters and amides include $-CO_2Alk^5$ [where Alk^5 is as previously defined] and $-CONR^5R^6$ [where R^5 and R^6 is each either a hydrogen atom or an optionally substituted C_{1-6}alkyl and each may be the same or different] groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide.

When, in compounds of formula (1), R^3 is present as an atom or group $-L^1(Alk^1)_tL^2(R^4)_u$ it may be present on any available carbon atom of the indole ring. When L^1 and/or L^2 is present in a group R^3 as a linker atom or group it may be any linker atom or group as previously defined for L^3. Alk^1, when present in the atom or group R^3 may be any aliphatic or heteroaliphatic chain as defined hereinbefore.

When the groups R^5 and R^6 or R^6 and R^7 are present in R^3 groups in compounds of formula (1) these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from –O-, -S- or $-N(R^5)$-. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

Examples of the R^3 substituents represented by $-L^1(Alk^1)_tL^2(R^4)_u$ when present in Ar^1 groups in compounds of the invention include atoms or groups $-L^1Alk^1L^2R^4$, $-L^1Alk^1R^4$, $-L^1R^4$ and $-Alk^1R^4$ wherein L^1, Alk^1, L^2 and R^4 are as defined above. Particular examples of such substituents include $-L^1CH_2L^2R^4$,

$-L^1CH(CH_3)L^2R^4$, $-L^1CH(CH_2)_2L^2R^4$, $-L^1CH_2R^4$, $-L^1CH(CH_3)R^4$, $-L^1(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and $-R^4$ groups.

Thus the indole ring in compounds of formula (1) may be optionally substituted for example by one, two or three R^3 atoms or groups where R^3 is a halogen atom, e.g. fluorine, chlorine, bromine or iodine atom, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. $-CF_3$, $-CHF_2$, CH_2F, haloC_{1-6}alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^3$ [where Alk^3 is as defined above for Alk^5], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylamino-C_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonyl-amino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylamino-carbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino,

C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

It will be understood that when two or three R^3 groups are present in compounds of formula (1) these may be the same or different.

When the group R^1 is present in compounds of formula (1) as a C_{1-6}alkyl group it may be any C_{1-6}alkyl group as previously defined.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and base addition salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

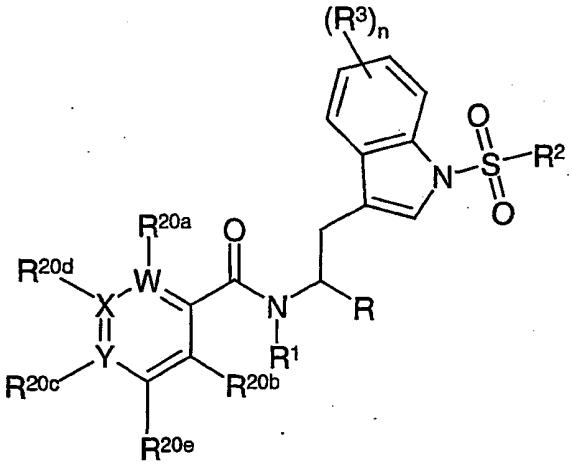
Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

Ar in compounds of the invention is preferably an optionally substituted phenyl or pyridyl group as hereinbefore defined.

One particular class of compounds of formula (1) is that wherein Alk is a $-CH(R)(CH_2)_m-$ group in which m is the integer 1.

A particularly useful group of compounds according to the invention has the formula (2):



(2)

wherein:

W, X and Y is each a carbon atom or one of W, X and Y is a nitrogen atom and the others are carbon atoms;

R^{20a}, R^{20b}, R^{20c}, R^{20d} and R^{20e} are each a hydrogen atom or an atom or group R^{13} as previously defined;

R, R^1, R^2, R^3 and n are as previously defined;

provided that when one of W, X and Y is a nitrogen atom it is not substituted by R^{20a}, R^{20d} or R^{20c} respectively;

and the salts, solvates, hydrates and N-oxides thereof.

R^1 in compounds of the invention is in particular a hydrogen atom.

R in compounds of the invention is preferably a carboxylic acid ($-CO_2H$) or a carboxylic acid ester ($-CO_2Alk^5$). Particularly useful Alk^5 groups include alkyl groups, especially methyl, ethyl and i-propyl groups. Most preferably R is a carboxylic acid ($-CO_2H$).

R^2 in compounds of the invention is preferably an optionally substituted C_{1-6}alkyl group. Most preferably R^2 is an optionally substituted methyl group, especially a methyl or ethyl group. Preferred optional substituents include one, two or three halogen atoms, especially fluorine or chlorine atoms

In general in compounds of formula (1) and (2) n is zero or the integer 1 or 2. When present R^3 is preferably a halogen atom or an C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy ($-OR^5$), haloC_{1-6}alkoxy, hydroxy, nitro, cyano or $-NR^5R^6$ group. Particularly useful halogen atoms include fluorine and chlorine atoms. Particularly useful C_{1-6}alkyl groups include methyl and ethyl groups, particularly useful haloC_{1-6}alkyl groups include $-CF_3$, particularly useful C_{1-6}alkoxy groups include methoxy and ethoxy groups and particularly useful haloC_{1-6}alkoxy groups include $-OCF_3$ groups. Particularly useful $-NR^5R^6$ groups include $-NHCH_3$ and $-N(CH_3)_2$ groups.

In compounds of formula (2) R^{20e} is preferably a hydrogen or halogen atom, especially a fluorine or chlorine atom. Most preferably R^{20e} is a hydrogen atom.

In another preferred class of compounds of formulae (1) and (2) W, X and Y is each an optionally substituted CH group. In one preferred group of compounds of this class R^{20a}, R^{20c} and R^{20d} is each a hydrogen atom and R^{20e} is as just defined. R^{20b} in this group of compounds is preferably a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluoromethoxy or nitro group. Most preferably R^{20b} is a chlorine atom. In another preferred group of compounds of this class R^{20c} and R^{20d} is each a hydrogen atom and R^{20e} is as just defined. R^{20a} and R^{20b} in this group of compounds is each preferably a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluromethoxy or nitro group. Most preferably R^{20a} and R^{20b} is each a chlorine atom. In another preferred group of compounds of this class R^{20d} is a hydrogen atom and R^{20e} is as just defined. In this group of compounds R^{20a} and R^{20b} is each preferably an atom or group selected from a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluoromethoxy or nitro group. In this group of compounds R^{20c} is preferably a group of formula $-CONHAlk^2R^{13a}$ or $-CSNHAlk^2R^{13a}$ as hereinbefore generally defined. In this group Alk^2 is preferably a $-CH_2-$ or $-CH_2CH_2-$ chain and R^{13a} is preferably an optionally phenyl, thienyl, furanyl, pyridyl or pyrimidinyl group where preferred optional substituents include those preferred atoms and groups as hereinbefore describe in relation to R^3.

In another preferred class of compounds of formulae (1) and (2) W and X is each an optionally substituted CH group and Y is a nitrogen atom. In this class of compounds R^{20c} is absent. In one preferred group of compounds of this class R^{20a} and R^{20d} is each a hydrogen atom and R^{20e} is as just defined. R^{20b} in this group of compounds is preferably a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy,

haloC_{1-6}alkoxy, especially trifluoromethoxy or nitro group. Most preferably R^{20b} is a chlorine atom. In another preferred group of compounds of this class R^{20d} is a hydrogen atom and R^{20e} is as just defined. R^{20a} and R^{20b} in this group of compounds is each preferably a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluoromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluoromethoxy or nitro group. Most preferably R^{20a} and R^{20b} is each a chlorine atom.

In another preferred class of compounds of formulae (1) and (2) X and Y is each an optionally substituted CH group and W is a nitrogen atom. In this class of compounds R^{20a} is absent, R^{20c} and R^{20d} is each preferably a hydrogen atom and R^{20b} is preferably a halogen atom, especially a fluorine or chlorine atom, or a methyl, trifluromethyl or nitro group. Most preferably R^{20b} is a chlorine atom.

In another preferred class of compounds of formulae (1) and (2) W and Y is each an optionally substituted CH group and X is a nitrogen atom. In this class of compounds R^{20d} is absent, R^{20a} is preferably a hydrogen or halogen, especially fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluromethoxy or nitro group, R^{20b} is preferably a hydrogen or halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluromethoxy or nitro group and R^{20c} is preferably a hydrogen or halogen atom, especially a fluorine or chlorine atom, or a C_{1-6}alkyl, especially methyl or ethyl, haloC_{1-6}alkyl, especially trifluromethyl, C_{1-6}alkoxy, especially methoxy or ethoxy, haloC_{1-6}alkoxy, especially trifluromethoxy or nitro group and R^{20e} is as just defined. Most preferably R^{20a} and R^{20c} is each a hydrogen atom, R^{20b} is a chlorine atom and R^{20e} is as just defined or R^{20a} is a chlorine atom and R^{20b} and R^{20c} is each a hydrogen atom and R^{20e} is as just defined

or R^{20a} is a chlorine atom, R^{20b} is a hydrogen atom and R^{20c} is a chlorine atom or methyl group.

Particularly useful compounds of the invention include:
(2*S*)-2-[(3,5-dichloropyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
(2*S*)-2-(2,6-dichlorobenzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
(2*S*)-2-[(2-chloropyridyl-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
2-[2-chloro-4-(3-hydroxy-benzylcarbamoyl)-benzoylamino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
2-(2,6-dichloro-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
2-[(3,5-dichloro-pyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent inhibitors of LFA-1 binding to cellular adhesion molecules, particularly ICAM-1, -2 or –3. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating LFA-1 mediated cell signalling and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inappropriate migration of cells. The invention extends to such a use and to the use of the compounds of formula (1) for the manufacture of a medicament for treating such diseases and disorders. Particular diseases include inflammatory diseases and immune disorders.

Particular uses to which the compounds of the invention may be put include the treatment or inhibition of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, systemis lupus

erythematosus, hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type 1 and uveitis, cutaneous manifestations of immunologically mediated illness such as inflammatory and hyperproliferative skin diseases (e.g. psoriasis, atopic dermatitis, alopecia aerata, allergic contact dermatitis, irritant contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erthema multiforme, cutaneous eosinophilias, lupus erythematosus, acne, granuloma annulare, pyoderma gangrenosum, sun burns and toxic epidermal necrolysis), inflammatory bowel disease, opthalmic inflammatory diseases or immune-mediated conditions of the eye, such as auto-immune diseases (e.g. keratoplasty and allergic keratitis), allergic conditions (e.g. vernal conjunctivitis), inflammatory conditions and corneal transplants. Compounds of formula (1) are further useful for the treatment and/or prevention of ischemia-reperfusion injury e.g myocardial infarction, stroke, gut ischemia, renal failure, graft vs. host and host vs. graft rejection, renal failure or hemorrhage shock, and infective diseases such as septic shock, adult respiratory distress syndrome or traumatic shock.

Especially preferred uses to which compounds of the invention may be put include the tretament or inhibition of cutaneous manifestations of immunologically mediated illness such as inflammatory and hyperproliferative skin diseases (e.g. psoriasis, atopic dermatitis, alopecia aerata, allergic contact dermatitis, irritant contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erthema multiforme, cutaneous eosinophilias, lupus erythematosus, acne, granuloma annulare, pyoderma gangrenosum, sun burns and toxic epidermal necrolysis), most especially psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, eczematous dermatitis or seborrhoeic dermatitis.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of formula (1) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formula (1) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temerature. Such materials include for example cocoa butter and polyethylene glycols.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active

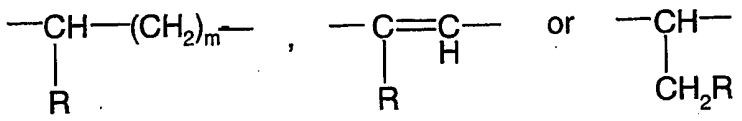
ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

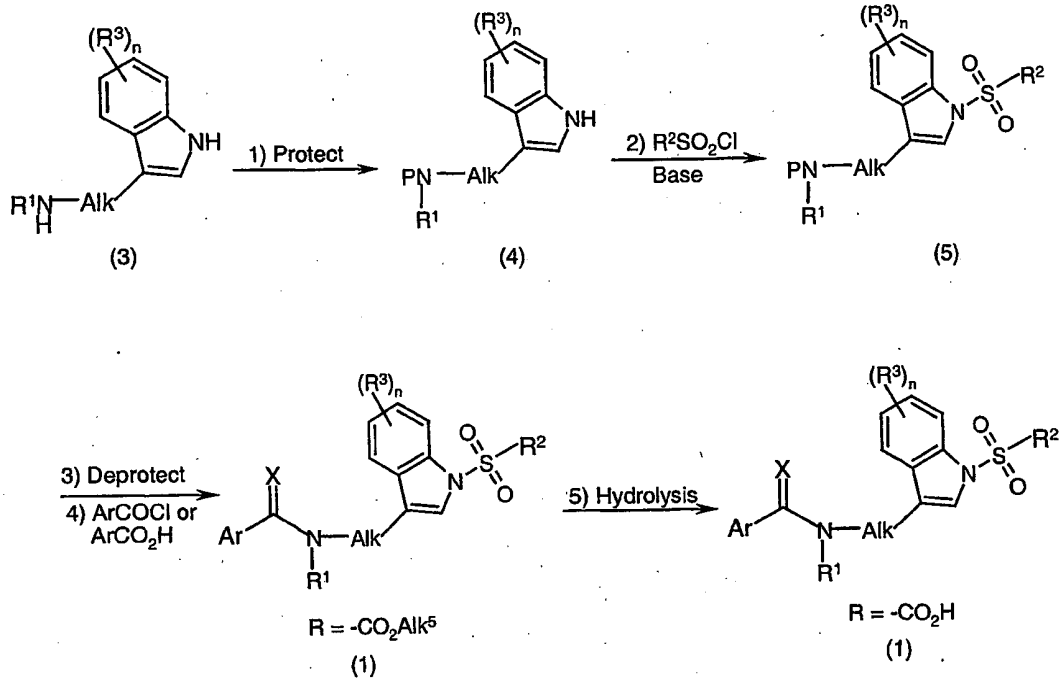
In the following process description, the symbols R^1, Alk, m, Alk^5, R^3, n, R^2, X, Ar, L^2, L^3, R^{14} and R^6 when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention a compound of formula (1) in which Alk is a chain



in which m is zero or the integer 1or 2 and R is a carboxylic acid (-CO_2H) may be prepared by the reactions illustrated in Scheme (1):

Scheme 1



(3) (4) (5) (1) (1)

An amino acid analogue of formula (3) in which R is a carboxylic acid ester (-CO_2Alk^5) in which for example Alk^5 is an alkyl group such as a methyl or ethyl group may be N-protected to yield an protected intermediate of formula (4) (P = protecting group) by any standard method for protection of amino acids such as those described in Greene (*ibid*), Bodansky, M. [Principles of Peptide Synthesis, 2nd ed., Springer-Verlag, Berlin (1993)] or Kocienski, P. J. [Protecting Groups, Thieme, Stuttgart (1994)]. Thus for example an amino acid intermediate of formula (3) may be N-protected with a t-butyloxycarbonyl group (P = BOC i.e. $(CH_3)_3COC(O)$-) by reaction with an anhydride (

$[(CH_3)_3COC(O)]_2O$) or a chloroformate $[(CH_3)_3CC(O)Cl]$ in an organic solvent such as a halogenated hydrocarbon e.g. dichloromethane, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane, a nitrile e.g. acetonitrile or an amide e.g. a substituted amide such as dimethylformamide optionally in the presence of water and a base such as a carbonate e.g. caesium or potassium carbonate or sodium hydrogen carbonate, a hydroxide e.g. sodium or potassium hydroxide or an amine e.g. triethylamine or N-methylmorpholine at a temperature from about 0°C to ambient temperature.

Amino acid intermediates of formula (3) are commercially available or may be formed by methods known in the literature, for example the methods of Cook, J. M. et al (Tetrahedron Lett., 1995, 7411-7414 and J. Org. Chem. 1997, 62, 7447-7456), Thiruvikraman, S. V. and Sakagami, Y. (Tetrahedron Lett., 1988, 2339-2342), Li, M. and Johnson, M. E. (Tetrahedron Lett., 1994, 6255-6258), Balsamini, C. et al (Synthesis, 1995, 370-372), Horwell, D. C. et al (J. Org. Chem., 1994, 59, 4418-4423), Ma, C et al (Tetrahedron Lett., 2000, 2781-2785), Morales-Rios, M. S. et al (Heterocycles, 1996, 43, 1483-1496) and Gademann, K. et al (Angew Chem Int Ed, 1999, 38, 1223-1226).

A sulphonamide derivative of formula (5) may be formed by reaction of a protected amino acid derivative of formula (4) with a sulphonating agent such as a sulphonyl halide (R^2SO_2Hal), for example methanesulphonyl chloride or an anhydride $[(R^2SO_2)_2O]$ such as trifluoromethanesulphonic anhydride in an organic solvent such as a halogenated hydrocarbon e.g. dichloromethane or an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane optionally in the presence of a base such as an amine e.g. triethylamine, N-methylmorpholine or pyridine or a hydroxide e.g. sodium or potassium hydroxide at a temperature from about –78°C to ambient temperature.

A sulphonamide of formula (5) may be N-deprotected by using any standard deprotection conditions depending on the nature of the protecting group P. Thus, for example, when P is a BOC group deprotection may be accomplished with an acid, for example an inorganic acid such as

hydrochloric acid or an organic acid such as trifluoroacetic acid, or a silane such as chlorotrimethylsilane in the presence of phenol optionally in an organic solvent such as a halogenated hydrocarbon e.g. dichloromethane at a temperature from around 0°C to around ambient temperature.

Subsequent to this deprotection step an amide of formula (1) (X = O, R = -CO_2Alk^5) may be formed by coupling the deprotected amine derived from a compound of formula (5) with an acid of formula (6):

$$ArCO_2H \qquad (6)$$

or an active derivative thereof.

Active derivatives of acids of formula (6) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters. Particular halides include chlorides.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane, at a low temperature e.g. around –30°C to around ambient temperature, optionally in the presence of a base e.g. an organic base such as amine e.g. triethylamine or pyridine or dimethylaminopyridine, or a cyclic amine such as N-methylmorpholine.

When an acid of formula (6) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexyl-carbodimide, advantageously in the presence of a catalyst compound such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a

chloroformate, for example ethyl chloroformate, prior to reaction with the amine of formula (6).

Thioamides of formula (1) (X = S, R = $-CO_2Alk^5$) may be prepared from amides of formula (1) by treatment with a thiation reagent, such as Lawesson's reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

A compound of formula (1) (R = $-CO_2H$) may be obtained from an ester of formula (1) (R = $-CO_2Alk^5$) by hydrolysis. The hydrolysis may be performed using either an acid or a base depending on the nature of Alk^5, for example an organic acid such as trifluoroacetic acid optionally in an organic solvent such as a halogenated hydrocarbon e.g. dichloromethane, or an inorganic base such as sodium, lithium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature to 60°C. Where desired, mixtures of such solvents may be used.

Where in the general processes described above intermediates such as esters of formulae (3), acids of formula $ArCO_2H$ and sulphonyl chlorides of formula R^2SO_2Cl are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds. Particular examples of such methods are given in the Examples hereinafter.

Thus intermediates of formula (3) and any other intermediates described herein required to obtain compounds of formula (1) may be prepared by methods known to those skilled in the art following procedures set forth in references such as *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-19 (John Wiley and Sons, 1999), *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis* Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's* Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and *March's* Advanced Organic Chemistry (John Wiley and Sons, 1992)

For example sulphonyl chlorides of formula R^2SO_2Cl may be formed by reaction of Grignard reagents of formula R^2MgHal where Hal is a halogen atom such as a chlorine, bromine or iodine atom or lithium reagents of formula R^2Li with sulfuryl chloride in an inert solvent such as a hydrocarbon e.g. pentane or hexane or an aromatic hydrocarbon e.g. toluene at a low temperature, for example about -65 to about -20°C.

Sulphonyl halides such as sulphonyl chlorides of formula R^2SO_2Cl may also be formed from sulphonic acids of formula R^2SO_2H by reaction with a halogenating agent such as a thionyl halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous trichloride or a phosphorous pentahalide such as phosphorous pentachloride optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to the reflux temperature.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-

butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile, a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as electrophile and an acid may be introduced by using carbon dioxide as electrophile. Aromatic acids of formula $ArCO_2H$ may also be generated by quenching Grignard reagents of formula ArMgHal with carbon dioxide. Aromatic acids of formula $ArCO_2H$ generated by this method may be converted to activated derivatives, e.g. acid halides by the methods just described for the conversion of sulphonic acids to sulphonyl halides.

Compounds of the invention and intermediates thereto such as compounds of formulae (3), (4), (5), $ArCO_2H$ and R^2SO_2Cl may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent $(R^4)_uL^2(Alk^1)_tZ^2$ in which Z^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a $-C(O)Z^3$, $C(S)Z^3$, $-N(R^{17})COZ^3$ or $-N(R^{17})C(S)Z^3$ group in which Z^3 is a leaving

atom or group as described for Z^2. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which Z^2 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzo-triazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which Z^2 is replaced by a -S(O)Hal or $-SO_2Hal$ group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which Z^2 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

Ester groups such as $-CO_2Alk^5$ and $-CO_2R^9$ in the compound of formula (1) and intermediates thereto may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the

group Alk^5. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^{14}$ [where R^{14} represents an alkyl group such as methyl group] in compounds of formula (1) and intermediates thereto may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{25}$ group (where R^{25} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. $-CO_2Alk^5$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^{14}$ group by coupling with a reagent $R^{14}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSR^6$ or $-CSNHR^6$ group may be prepared by treating a corresponding compound containing a $-NHCOR^6$ or $-CONHR^6$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohyride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles (-CN), for

example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney® nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

In another example, sulphur atoms in the compounds, for example when present in a group L^1 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent,such as a halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol at a temperature from the ambient temperature to the reflux temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

THF - tetrahydrofuran;	boc - butoxycarbonyl
DMF - dimethylformamide;	DMSO - dimethyl sulphoxide;
DCM - dichloromethane;	TFA - trifluoroacetic acid;
MeOH - methanol;	EtOH - ethanol
EtOAc - ethyl acetate.	nBuLi - n-butyllithium
RT - room temperature	Et_3N - triethylamine
sat. - saturated	HOBT - 1-hydroxybenzotriazole hydrate
NMM - 4-methylmorpholine	ether - diethyl ether
DIEA - diisopropylethylamine	t.l.c. – thin layer chromatography

EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

PS-Trisamine - Tris-(2-aminoethyl)amine polystyrene

MP-TsOH - Macroporous polystyrene sulfonic acid

All NMRs were obtained at 300MHz unless otherwise indicated.

Intermediate 1

(*2S*)-2-*tert*-Butoxycarbonylamino-3-(1*H*-indol-3-yl)-propionic acid methyl ester

A solution of di-*tert*-butyl dicarbonate (8.72g, 40.0mmol) in dioxane (200ml) was added to a suspension of *L*-tryptophan methyl ester hydrochloride (10.18g, 40.0mmol) and sodium hydrogen carbonate (16.8g, 200mmol) in water (150ml). The mixture was stirred at RT for 5 h. The dioxane was removed *in vacuo*, water (50ml) added to the residue which was then extracted with EtOAc (300ml + 100ml). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid (12.54 g, 98%). δ_H ($CDCl_3$) 8.11 (1H, br s), 7.55 (1H, d, *J* 7.9Hz), 7.35 (1H, d, *J* 8.1Hz), 7.22-7.10 (2H, m), 7.00 (1H, d, *J* 2.3Hz), 5.07, (1H, br m), 4.67 (1H, br m), 3.68 (3H, s), 3.30 (2H, m) and 1.53 (9H, br s); *m/z* (ES^+) 341.1 (*MNa^+*).

Intermediate 2

(*2S*)-2-*tert*-Butoxycarbonylamino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

Methanesulfonyl chloride (1.46ml, 18.85mmol) was added over 15min to a solution of Intermediate 1 (6.0g, 18.85mmol) and Et_3N (5.25ml, 37.7mmol) in CH_2Cl_2 (100ml). After 2h at RT more methanesulfonyl chloride (1.46ml, 18.85mmol) was added. After a further 18 h more triethylamine (2.8ml) and methanesulfonyl chloride (1.46ml, 18.85mmol) were added. After a further 4h the solution was washed with 1M HCl (100ml) and sat. $NaHCO_3$ (100ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2; 1-2% acetone in DCM) gave the title compound as a colourless gum (2.6 g, 35%). δ_H ($CDCl_3$) 7.90 (1H, d, *J* 7.5Hz), 7.58 (1H, d, *J* 7.1Hz), 7.38-7.31 (2H, m), 7.24 (1H, s), 4.99 (1H, br m), 4.66 (1H, br m), 3.71 (3H, s), 3.39-3.36 (1H, m), 3.29-3.26 (1H, m), 3.05 (3H, s), 1.43 (9H, s); *m/z* (ES^+) 419.2 (*MNa^+*).

Intermediate 3

(*2S*)-2-Amino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester hydrochloride

Intermediate 2 (2.60g, 6.54mmol) was treated with 2.6M HCl in EtOAc (75ml) for 4h at RT. Volatiles were removed *in vacuo* and the residue triturated with Et_2O (50ml). The pale pink-purple solid was filtered off, washed with Et_2O and dried to give the title compound (1.60 g, 74%). δ_H (d_6-DMSO) 8.53 (2H, br s, NH_2), 7.63 (1H, d, *J* 8.0Hz), 7.45 (1H, d, *J* 7.9Hz), 7.35 (1H, s), 7.23-7.11 (2H, m), 4.17 (1H, t, *J* 6.3Hz), 3.49 (3H, s), 3.20 (3H, s) and 3.13-3.11 (2H, m).

Intermediate 4

(*2S*)-2-[(2-Chloropyridine-3-carbonyl)-amino]-3-(1*H*-indol-3-yl)-propionic acid methyl ester

A solution of 2-chloronicotinoyl chloride (1.0g, 5.7mmol) in dioxane (10ml) was added slowly to a mixture of *L*-tryptophan methyl ester hydrochloride (1.59g, 6.23mmol), $NaHCO_3$ (1.43g, 17.0mmol), water (20ml) and dioxane (10ml). After 4 h at RT more $NaHCO_3$ (400mg) and 2-chloronicotinoyl chloride (300mg) were added. After a further 30min the dioxane was removed *in vacuo* and the aqueous residue extracted with DCM. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a white solid (2.5 g). δ_H ($CDCl_3$) 8.43 (1H, dd, *J* 4.8, 2.0Hz), 8.11 (1H, s), 8.00 (1H, dd, *J* 7.7, 2.0Hz), 7.57 (1H, d, *J* 7.8Hz), 7.35 (1H, d, *J* 8.1Hz), 7.29 (1H, dd, *J* 7.7, 4.8Hz), 7.19 (1H, t, *J* 7.0Hz), 7.12-7.07 (3H, m), 5.12 (1H, m), 3.75 (3H, s), 3.52 (1H, dd, *J* 5.8, 14.5Hz) and 3.43 (1H, dd, *J* 5.5, 15.0Hz); *m/z* (ES^+) 358.1 (MH^+).

Intermediate 5

(*2S*)-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(1*H*-indol-3-yl)-propionic acid methyl ester

Et_3N (2.2ml, 15.7mmol) and phthalic anhydride (1.3g, 8.6mmol) were added to tryptophan methyl ester hydrochloride (2.0g, 7.9mmol) in toluene (25ml).

The mixture was heated at reflux for 3 days. The solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, DCM) gave the title compound as a yellow solid (2.52g, 92%). δ_H ($CDCl_3$) 8.02 (1H, br s), 7.78-7.72 (2H, m), 7.69-.763 (2H, m), 7.60 (1H, d, *J* 7.7Hz), 7.28-7.25 (1H, m), 7.15-7.00 (3H, m), 5.30-5.25 (1H, m), 3.80 (3H, s), 3.77-3.74 (2H, m).

Intermediate 6

(2*S*)-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(1-ethanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

n-Butyl lithium (2.5M in hexanes, 460µl, 1.15mmol) was added to a solution of Intermediate 5 (200mg, 0.57mmol) in THF (2ml) at -78°C. After 15 min, ethanesulfonyl chloride (109µl, 1.15mmol) was added and the mixture allowed to warm slowly to RT overnight. The mixture was diluted with ether (20ml) and washed with sat. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM) gave the title compound as a white solid (127mg, 50%). *m/z* (ES^+) 441.1 (MH^+).

Intermediate 7

(2*S*)-2-Amino-3-(1-ethanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

A mixture of Intermediate 6 (117mg, 0.27mmol) and hydrazine monohydrate (14µl, 0.29mmol) in abs. EtOH (4ml) was stirred for 2h at RT then heated at reflux overnight. The mixture was cooled to 0°C then filtered. The filtrate was concentrated *in vacuo*, purification by column chromatography (SiO_2, 1% to 2% MeOH in DCM) gave the title compound, as a mixture with the corresponding ethyl ester, as a colourless oil (68mg, 82%). δ_H ($CDCl_3$) 7.89-7.86 (1H, m), 7.63-7.59 (1H, m), 7.37-7.26 (3H, m), 4.18-4.08 (1H, m), 3.84-3.77 (m), 3.68 (s), 3.26 (2H, q, *J* 7.4Hz), 3.22-3.15 (1H, m), 3.00 (1H, dd, *J* 7.4, 14.5Hz), 1.21 (t, *J* 7.2Hz), 1.18 (3H, t, *J* 7.4Hz); *m/z* (ES^+) 311.1 (MH^+ Me ester) 325.1 (MH^+ Et ester).

Intermediate 8

1-Methanesulfonyl-1*H*-indole-3-carbaldehyde

1*H*-indole-3-carbaldehyde (14.5g, 100mmol) in DMF (100ml) was added to a suspension of sodium hydride (60% in oil, 4.4g, 110mmol) in DMF (150ml) at 0°C. After 1h, methane sulfonyl chloride (8.51ml, 110mmol) was added slowly. The mixture was stirred at 0°C for 2h then at RT for 2h. Water was added to quench and the solvent removed *in vacuo*. The residue was dissolved in DCM, washed with water (x 2), dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from EtOAc gave the title compound as brown crystals (9.2g). δ_H (d_6-DMSO) 10.09 (1H, s), 8.61 (1H,s), 8.20-8.17 (1H, m), 7.92-7.89 (1H, m), 7.53-7.42 (2H, m), 3.67 (3H, m); *m/z* (ES^+) 224 (MH^+).

Intermediate 9

2-*tert*-Butoxycarbonylamino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-acrylic acid methyl ester

A mixture of Intermediate 8 (7.0g, 31.4mmol), *tert*-Butoxycarbonylamino-(diethoxy-phosphoryl)-acetic acid methyl ester (10.2g, 31.4mmol) and DBU (4.69ml, 31.4mmol) in DCM (150ml) was stirred at RT for 24h. The mixture was diluted with DCM (200ml), washed 1M HCl, dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from EtOAc gave the title compound as pale yellow needles (7.65g, 62%). δ_H (d_6-DMSO) 8.76 (1H, br s), 8.00 (1H, s), 7.88-7.85 (2H, m), 7.48-7.35 (3H, m), 3.76 (3H, s), 3.49 (3H, s), 1.40 (9H, s); *m/z* (ES^+) 417 (MH^+).

Intermediate 10

2-*tert*-Butoxycarbonylamino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

Wilkinson's catalyst (117mg, 1mol%) was added to a suspension of Intermediate 9 (5.0g, 12.7mmol) in MeOH (200ml). The mixture was hydrogenation in a Parr apparatus at 50 p.s.i. at 50°C for 24h. More catalyst (117mg) was added and hydrogenation continued as before for 24h. The solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, EtOAc) gave the title compound as a brown solid (4.62g, 92%). δ_H (d_6-DMSO, 400 MHz) 7.81 (1H, d, *J* 8.1Hz), 7.65 (1H, d, *J* 7.4Hz), 7.45-7.31 (4H,

m), 4.33-4.27 (1H, m), 3.63 (3H, s), 3.31 (3H, s), 3.14 (1H, dd, *J* 4.7, 14.7Hz), 3.02 (1H, dd, *J* 9.9, 14.7Hz), 1.32 (9H, s); *m/z* (ES^+) 419.2 (*MNa*$^+$).

Intermediate 11

2-Amino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester hydrochloride

Gaseous HCl was bubbled through a solution of Intermediate 10 (4.62g, 11.7mmol) in EtOAc (100ml) for a few seconds. The mixture was stirred at RT for 30min. The mixture was re-treated with HCl until reaction was complete as judged by t.l.c. The solid was filtered off and dried to give the title compound as a white solid (3.41g, 88%). δ_H (d_6-DMSO, 400 MHz) 8.72 (3H, br s), 7.87 (1H, d, *J* 8.2Hz), 7.69 (1H, d, *J* 7.7Hz), 7.59 (1H, s), 7.46-7.36 (2H, m), 4.41 (1H, t, *J* 6.4Hz), 3.74 (3H, s), 3.43 (3H, s), 3.3 (2H, obscured by HOD signal); *m/z* (ES^+) 297.0 (*MH*$^+$).

Intermediate 12

2-Chloro-terephthalic acid 4-methyl ester

A solution of boron tribromide (1M in DCM, 38.9ml, 38.9mmol) was added slowly to dimethyl chlorophthalate (8.9g, 38.9mmol) in DCM (200ml) at -50°C. The mixture was allowed to warm to RT overnight then poured onto ice and partitioned with EtOAc. The organic phase was concentrated *in vacuo*, the residue dissolved in aq $NaHCO_3$ and extracted with DCM. The aqueous phase was acidified with c.HCl to pH1 and the solid filtered off and dried to give the title compound as a white solid (contaminated with corresponding diacid) (8.4g). δ_H (d_6-DMSO) 8.05-7.84 (3H, m), 3.88 (3H, s); *m/z* (ES^+) 214.9 (*MH*$^+$).

Intermediate 13

2-Chloro-terephthalic acid 1-*tert*-butyl ester 4-methyl ester

N,N-Dimethylformamide di-*tert*-butyl acetal (38ml, 160mmol) was added slowly at reflux to a suspension of Intermediate 12 (8.24g, 38mmol) in toluene (100ml). The mixture was heated at reflux for a further 3h then diluted with EtOAc, washed with aq. $NaHCO_3$, water and brine, dried

(Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7% EtOAc in hexane) gave the title compound as a colourless oil (6.13g, 60%). δ_H($CDCl_3$) 8.07 (1H, d, *J* 1.6Hz), 7.93 (1H, dd, *J* 1.6, 8.1Hz), 7.74 (1H, d, *J* 8.1Hz), 3.94 (3H, s), 1.61 (9H, s); *m/z* (ES^+) 293 (*MNa^+*).

Intermediate 14

2-Chloro-terephthalic acid 1-*tert*-butyl ester

Lithium hydroxide monohydrate (1.40g, 33.3mmol) was added to a solution of Intermediate 13 (6.0g, 22.2mmol) in THF/water (3:1, 100ml). After 90min at RT the THF was removed *in vacuo*. The aqueous residue was diluted with water and extracted with ether. The aqueous phase was acidified with c.HCl and extracted with DCM. The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid (5.44g, 96%). δ_H (d_6-DMSO) 13.55 (1H, br s), 7.92-7.60 (2H, m), 7.79 (1H, d, *J* 7.9Hz), 1.55 (9H, s); *m/z* (ES^+) 279 (*MNa^+*).

Intermediate 15

2-Chloro-*N*-(3-methoxy-benzyl)-terephthalamic acid *tert*-butyl ester

EDC was added to a mixture of Intermediate 14 (5.44g, 21mmol), 3-methoxybenzylamine (2.88g, 21mmol), HOBT (3.12g, 23.1mmol) and NMM (2.54g, 23.1mmol) in DCM (100ml). The mixture was stirred overnight at RT then diluted with DCM, washed with 2M HCl, aq. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from EtOAc gave the title compound as white needles (5.99g, 76%). δ_H (d_6-DMSO) 9.22 (1H, br t, *J* 5.8Hz), 8.00 (1H, d, *J* 1.6Hz), 7.90 (1H, dd, *J* 1.6, 8.1Hz), 7.78 (1H, d, *J* 8.0Hz), 7.23 (1H, t, *J* 7.3Hz), 6.89-6.87 (2H, m), 6.82-6.79 (1H, m), 4.44 (2H, d, *J* 5.7Hz), 3.72 (3H, s), 1.54 (9H, s); *m/z* (ES^+) 376 (*MH^+*).

Intermediate 16

2-Chloro-*N*-(3-hydroxy-benzyl)-terephthalamic acid

Boron tribromide (1M in DCM, 3.99ml, 3.99mmol) was added dropwise to a solution of Intermediate 15 (500mg, 1.33mmol) in DCM at -5°C. The mixture was stirred at RT overnight then partitioned between EtOAc and water. The

organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a yellow oil (509mg). δ_H (d_6-DMSO) 9.31 (1H, br s), 9.21 (1H, t, *J* 5.9Hz), 8.01 (1H, d, *J* 1.4Hz), 7.92-7.84 (2H, m), 7.10 (1H, t, *J* 8.1Hz), 6.74-6.71 (2H, m), 6.64-6.60 (1H, m), 4.39 (2H, d, *J* 5.9Hz); *m/z* (ES^+) 306 (MH^+).

Intermediate 17

(1-Methanesulfonyl-1*H*-indol-3-yl)-methanol

Sodium borohydride (851mg, 22.4mmol) was added in portions to a suspension of Intermediate 8 (2.50g, 11.2mmol) in abs. EtOH (25ml) at 0°C. After 2h at RT, the solvent was removed *in vacuo*. Aq. NaOH (1M) was added to the residue and the mixture extracted with ether (x 2). The ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid (2.49g, quant). δ_H (d_6-DMSO) 7.81 (1H, d, *J* 8.2Hz), 7.71 (1H, d, *J* 7.1 Hz), 7.44 (1H, s), 7.40-7.27 (2H, m), 5.13 (1H, br s), 4.65 (2H, s), 3.36 (3H, s); *m/z* (ES^+) 207.9 (M^+-(H_2O)).

Intermediate 18

3-Bromomethyl-1-methanesulfonyl-1*H*-indole

Anhydrous HBr was bubbled through a suspension of Intermediate 17 (2.45g, 10.9mmol) in ether (100ml) for a few minutes. The mixture was then stirred at RT for 20 min. The solvent was removed *in vacuo* to give the title compound as a pink solid. δ_H (d_6-DMSO) 7.95-7.75 (3H, m), 7.48-7.35 (2H, m), 4.95 (2H, s), 3.47 (3H, s); *m/z* (ES^+) 208 (M^+-*Br*).

Intermediate 19

2-Amino-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid ethyl ester

A solution of LDA (2M, 6.0ml, 12mmol) was added to a solution of *N*-(diphenylmethylene)glycine ethyl ester (2.91g, 10.9mmol), in THF (70ml) at -78°C. After 1h a solution of Intermediate 18 (3.14g, 10.9mmol) in THF (30ml) was added. The mixture was stirred for 2h at -78°C then allowed to warm to RT over 2h. Water was added, the bulk of the THF removed *in vacuo* and the residue partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to

give a light brown gum. This was dissolved in THF (100ml) and treated with 1M HCl (100ml). After 30min the THF was removed *in vacuo*. The aqueous residue was extracted with ether (3 x 100ml), basified with NaOH (pH10) and extracted with DCM. The DCM extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a yellow oil (2.03g). δ_H (d_6-DMSO) 7.80 (1H, d, *J* 7.5Hz), 7.64 (1H, d, *J* 7.0Hz), 7.38 (1H, s), 7.37-7.27 (2H, m), 4.00 (2H, q, *J* 7.1Hz), 3.65 (1H, t, *J* 6.6Hz), 3.32 (3H, s), 3.00 (1H, dd, *J* 6.1, 14.4Hz), 2.90 (1H, dd, *J* 7.1, 14.4Hz), 1.84 (2H, br s), 1.08 (3H, t, *J* 7.2Hz); *m/z* (ES^+) 311 (MH^+).

Example 1

(2*S*)-2-[(3,5-Dichloropyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

A solution of 3,5-dichloroisonicotinoyl chloride (168mg, 0.8mmol), Intermediate 3 (250mg, 0.75mmol) and Et_3N (111µl, 0.8mmol) in DCM (15ml) was stirred a RT for 5 h. The mixture was diluted with DCM (50ml), washed with sat. $NaHCO_3$ (50ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white foam (376 mg, 100%). δ_H ($CDCl_3$) 8.95 (2H, s), 7.89 (1H, d, *J* 8.3Hz), 7.66 (1H, d, *J* 8.3Hz), 7.43-7.28 (3H, m), 6.74 (1H, br d, *J* 7.5Hz), 5.27-5.20 (1H, m), 3.77 (3H, s), 3.44-3.38 (2H, m) and 3.08 (3H, s).

Example 2

(2*S*)-2-(2,6-Dichlorobenzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

A solution of 2,6-dichlorobenzoyl chloride (160mg, 0.75mmol), Intermediate 3 (250mg, 0.75mmol) and Et_3N (210µl, 1.5mmol) in DCM (15ml) was stirred a RT for 2h. The mixture was diluted with DCM (60ml), washed with 2M HCl (50ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white foam (375mg, 100%). δ_H ($CDCl_3$) 7.90 (1H, d, *J* 7.9Hz), 7.69 (1H, d, *J* 8.4Hz), 7.41-7.27 (6H, m), 6.48 (1H, br d, *J* 7.6Hz), 5.27-5.23 (1H, m), 3.73 (3H, s), 3.42 (2H, d, *J* 5.7Hz) and 3.07 (3H, s).

Example 3

(2*S*)-2-[(2-Chloropyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

Methanesulfonyl chloride (195µl, 2.5mmol) was added to a solution of Intermediate 4 (750mg, 2.1mmol) and Et_3N (350µl, 2.5mmol) in DCM (11ml) and the mixture stirred at RT. A further 2 equivalents of methane sulfonyl chloride and Et_3N were added in portions during the course of the 16h reaction. The mixture was diluted with DCM (10ml), washed with sat. $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2; 1.5% MeOH in DCM) gave the title compound as a yellow solid (144mg). δ_H ($CDCl_3$) 8.47 (1H, dd, *J* 4.7, 2.0Hz), 8.04 (1H, dd, *J* 7.7, 2.0Hz), 7.90 (1H, d, *J* 8.3Hz), 7.61 (1H, d, *J* 7.7Hz), 7.38-7.14 (5H, m), 5.16-5.14 (1H, m), 3.77 (3H, s), 3.47 (1H, dd, *J* 14.6, 5.7Hz), 3.37 (1H, dd, *J* 14.6, 5.7Hz) and 3.05 (3H, s); *m/z* (ES^+) 436.1 (MH^+).

Example 4

(2*S*)-2-[(3,5-Dichloropyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

Lithium hydroxide monohydrate (33.6mg, 0.8mmol) was added to the compound of Example 1 (356mg, 0.75mmol) in a mixture of THF (10ml) and water (10ml). After 6h at RT the mixture was concentrated *in vacuo*. The residue was diluted with water and acidified with 2M HCl (1ml). The precipitate was filtered off, washed with water and dried to give the title compound as a white solid (168mg, 49%). δ_H (d_6-DMSO) 12.95 (1H, br s), 9.32 (1H, d, *J* 8.0Hz), 8.65 (2H, s), 7.82 (1H, d, *J* 8.0Hz), 7.72 (1H, d, *J* 7.3Hz), 7.45 (1H, s), 7.42-7.33 (2H, m), 4.87-4.81 (1H, m), 3.31 (3H, s), 3.31-3.28 (1H, m) and 3.16-3.10 (1H, m); *m/z* (ES^+) 456 (MH^+).

Example 5

(2*S*)-2-(2,6-Dichlorobenzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From the compound of Example 2 by the method of Example 4.

White solid (243mg, 67%). δ_H (d_6-DMSO) 12.80 (1H, br s), 9.12 (1H, d, *J* 8.0Hz), 7.81 (1H, d, *J* 7.9Hz), 7.71 (1H, d, *J* 7.9Hz), 7.45-7.32 (6H, m), 4.82-4.77 (1H, m), 3.31 (3H, s), 3.29-3.24 (1H, m), 3.10 (1H, dd, *J* 9.6, 15.3Hz); *m/z* (ES^+) 455.0 (MNa^+).

Example 6

(2*S*)-2-[(2-Chloropyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From the compound of Example 3 by the method of Example 4.

Off-white solid (108 mg, 77%). δ_H (d_6-DMSO) 12.90 (1H, br s), 8.87 (1H, d, *J* 8.0Hz), 8.26 (1H, dd, *J* 4.8, 2.0Hz), 7.63 (1H, d, *J* 7.5Hz), 7.54-7.47 (2H, m), 7.30-7.12 (4H, m), 4.59-4.52 (1H, m), 3.09-2.89 (2H, m) and 3.13 (3H, s); *m/z* (ES^+) 422.0 (MH^+).

Example 7

(2*S*)-2-[(2,4-Dichloropyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

A mixture of Intermediate 3 (149mg, 0.45mmol), HOBT (77mg, 0.57mmol), NMM (125µl, 1.14mmol), 2,4-dichloronicotinic acid (78mg, 0.41mmol) and EDC (109mg, 0.57mmol) in DCM (4.5ml) was stirred at RT for 5h. The mixture was diluted with DCM and washed with 2M HCl, sat. $NaHCO_3$ and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1% to 5% MeOH in DCM) gave the title compound as a white solid (187mg, 88%). δ_H (CDCl3) 8.04 (1H, d, *J* 8.1Hz), 7.92 (1H, d, *J* 8.2Hz), 7.61 (1H, d, *J* 9.0Hz), 7.43-7.28 (4H, m), 7.18 (1H, br d), 5.15 (1H, dt, *J* 7.1, 5.7Hz), 3.79 (3H, s), 3.51 (1H, dd, *J* 5.7, 14.8Hz), 3.37 (1H, dd, *J* 5.7, 14.8Hz), 3.08 (3H, s); *m/z* (ES^+) 469.9 (MH^+).

Example 8

(2*S*)-2-[(2,4-Dichloropyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From the compound of Example 7 by the method of Example 4. δ_H (d_6-DMSO) 9.06 (1H, d, *J* 7.9Hz), 7.80 (1H, d, *J* 7.9Hz), 7.74-7.69 (2H, m), 7.61 (1H, d, *J* 8.0Hz), 7.43 (1H, s), 7.40-7.29 (2H, m), 4.72 (1H, m), 3.3 (3H, s),

3.3 (1H, signal obscured), 3.11 (1H, dd, *J* 9.4, 15.1Hz); *m/z* (ES^+) 455.9 (MH^+).

Example 9

(2*S*)-2-[(2-Chloropyridine-3-carbonyl)-amino]-3-(1-ethanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

2-Chloronicotinoyl chloride (39mg, 0.22mmol) was added to a solution of Intermediate 7 (68mg, 0.21mmol) and Et_3N (31µl, 0.22mmol) in THF (4ml). After 15 min the solvent was removed *in vacuo*, the residue partitioned between EtOAc and water and the aqueous phase re-extracted with EtOAc. The combined organics were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% MeOH in DCM) gave the title compound, as a mixture with the corresponding ethyl ester, as a colourless oil. δ_H (CDCl3) 8.40 (1H, dd, *J* 2.0, 4.8Hz), 7.97 (1H, dd, *J* 2.0, 7.6Hz), 7.86-7.83 (1H, m), 7.61-7.57 (1H, m), 7.35-7.23 (5H, m), 5.14-5.06 (1H, m), 4.23-4.12 (m), 3.73 (s), 3.46 (1H, dd, *J* 5.9, 14.8Hz), 3.34 (1H, dd, *J* 5.8, 14.8Hz), 3.25 (2H, q, *J* 7.4Hz), 1.23 (3H, t, *J* 7.2Hz), 1.14 (t, *J* 6.8Hz).

Example 10

(2*S*)-2-[(2-Chloropyridine-3-carbonyl)-amino]-3-(1-ethanesulfonyl-1*H*-indol-3-yl)-propionic acid

From the compound of Example 9 by the method of Example 4.

Light pink solid. δ_H (d_6-DMSO, 400MHz, 350K) 8.70 (1H, d, *J* 8.0Hz), 8.44 (1H, dd, *J* 1.9, 4.8Hz), 7.86-7.84 (1H, m), 7.74-7.69 (2H, m), 7.47-7.40 (2H, m), 7.38-7.31 (2H, m), 4.80 (1H, dt, *J* 5.3, 8.4Hz), 3.47 (2H, q, *J* 7.3Hz), 3.34 (1H, dd, *J* 4.4, 15.1Hz), 3.19 (1H, dd, *J* 8.9, 15.1Hz), 1.08 (3H, t, *J* 7.3Hz); *m/z* (ES^+) 436.1 (MH^+).

Example 11

2-[2-Chloro-4-(3-hydroxy-benzylcarbamoyl)-benzoylamino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid methyl ester

EDC (106mg, 0.55mmol) was added to a mixture of Intermediate 16 (153mg, 0.5mmol), Intermediate 11 (166mg, 0.5mmol), HOBT (74mg, 0.55mmol) and NMM (115µl, 1.05mmol) in DMF (5ml). The mixture was stirred at RT overnight. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with 2M HCl, aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Trituration with 5% MeOH in DCM gave a solid which was filtered off and dried to give the title compound as a white solid (207mg, 71%). δ_H (d_6-DMSO) 9.30 (1H, s), 9.15 (1H, br t), 9.07 (1H, d, *J* 7.8Hz), 7.95 (1H, d, *J* 1.6Hz), 7.86-7.81 (2H, m), 7.70 (1H, d, *J* 7.0Hz), 7.47 (1H, s), 7.42-7.32 (3H, m), 7.10 (1H, t, *J* 8.0Hz), 6.72-6.70 (2H, m), 6.62 (1H, d, *J* 9.2Hz), 4.82-4.78 (1H, m), 4.38 (2H, br), 3.69 (3H, s), 3.32 (3H, s), 3.3 (1H, obscured by HOD), 3.16 (1H, dd, *J* 10.8, 14.2Hz); *m/z* (ES^+) 584.0 (MH^+).

Example 12

2-[2-Chloro-4-(3-hydroxy-benzylcarbamoyl)-benzoylamino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From the compound of Example 11 by the method of Example 4.

White solid. δ_H (d_6-DMSO, 400MHz) 13.13 (1H, br s), 9.46 (1H, br s), 9.30 (1H, t, *J* 5.9Hz), 9.08 (1H, d, *J* 8.0Hz), 8.09 (1H, d, *J* 1.4Hz), 8.01-7.96 (2H, m), 7.87 (1H, d, *J* 7.7Hz), 7.61 (1H, s), 7.56-7.47 (3H, m), 7.25 (1H, t, *J* 7.9Hz), 6.87-6.85 (2H, m), 6.78-6.76 (1H, m), 4.91-4.86 (1H, m), 4.53 (2H, d, *J* 5.8Hz), 3.45 (3H, s), 3.4 (1H, obscured by HOD), 3.28 (1H, dd, *J* 10.0, 15.0Hz); *m/z* (ES^+) 570.0 (MH^+).

Solution phase parallel synthesis general method

Reaction of a variety of (hetero)aryl acid chloride (prepared from corresponding acid if necessary) with the amino ester Intermediate 19, followed by ester hydrolysis and purification to give the acids.

The (hetero)aryl acid (0.15mmol) in DCM was treated with oxalyl chloride (26µl, 0.3mmol) for 3-4h at RT. The solvent and excess reagent were removed *in vacuo* to give the acid chloride.

A solution of Intermediate 19 (31mg, 0.1mmol) in THF (0.5ml) was added to a mixture of the acid chloride (0.3mmol) and DIEA (35 µl, 0.2mmol) in THF

(1.5ml). After 2.5h at RT, PS-Trisamine (80mg, 0.3mmol) and MP-TsOH (280mg, 0.4mmol) were added. After 3h at RT the resins were filtered off and washed with THF (4 x 0.5ml). Lithium hydroxide monohydrate (4.2mg, 0.1mmol) in water (0.5ml) was added to the filtrate. After 2h at RT, glacial acetic acid (12 µl, 0.2mmol) was added then the mixture concentrated *in vacuo*. Purification by HPLC gave the series of acids listed below.

Analytical HPLC method used for characterisation

Equipment:	Hewlett Packard 1100 LC/MSD		
Method:	Mobile Phase	A:- 0.1% formic acid	
		B:- 0.1% formic acid in acetonitrile	
	Gradient:-	Time(min)	%B
		Initial	5
		3.0	95
		5.0	95
		5.5	5
	Stop	7.00	
	Flow Rate:	0.9 ml/min	
	Column Temp:	40°C	
	Column:	Phenomenex Luna 3µ C_{18}(2) 50 x 4.6mm	
Detection	UV DAD	210 – 450nm step 2nm	
	MS	ES+ve	
	Mode scan	120 – 1000	
	Peak width	0.1min^{-1}	
	Fragmentor	80V	
	Drying gas flow rate	13.0l/min	
	Nebuliser Pressure	50 psig	
	Drying gas temperature	350°C	
Software	Chemstation Software Vs8.03		

Example 13

3-(1-Methanesulfonyl-1*H*-indol-3-yl)-2-[(2-methoxy-pyridine-3-carbonyl)-amino]-propionic acid

From 2-methoxy-nicotinic acid. Retention time 3.235 min; *m/z* (ES^+) 418.0 (MH^+).

Example 14

2-(2-Chloro-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2-chloro-benzoic acid. Retention time 3.307 min; *m/z* (ES^+) 421.0 (MH^+).

Example 15

3-(1-Methanesulfonyl-1*H*-indol-3-yl)-2-(2-trifluoromethyl-benzoylamino)-propionic acid

From 2-trifluoromethyl-benzoic acid. Retention time 3.396 min; *m/z* (ES^+) 455.0 (MH^+).

Example 16

2-(2,6-Dimethoxy-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2,6-dimethoxy-benzoic acid. Retention time 3.188 min; *m/z* (ES^+) 447.0 (MH^+).

Example 17

2-[(2-Chloro-6-methyl-pyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2-chloro-6-methyl-nicotinic acid. Retention time 3.115 min; *m/z* (ES^+) 436.0 (MH^+).

Example 18

2-(2-Bromo-5-nitro-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2-bromo-5-nitro-benzoic acid. Retention time 3.421 min; *m/z* (ES^+) 511.9 (MH^+).

Example 19

2-[(2-Ethylsulfanyl-pyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2-ethylsulfanyl-nicotinic acid. Retention time 3.365 min; *m/z* (ES^+) 448.0 (MH^+).

Example 20

2-(2,6-Dichloro-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2,6-dichloro-benzoyl chloride. Retention time 3.359 min; *m/z* (ES^+) 455.0 (MH^+).

Example 21

2-[(3,5-Dichloro-pyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 3,5-dichloro-isonicotinoyl chloride. Retention time 3.191 min; *m/z* (ES^+) 456.0 (MH^+).

Example 22

2-[(2-Chloro-pyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid

From 2-Chloro-nicotinoyl chloride. Retention time 3.037 min; *m/z* (ES^+) 422.0 (MH^+).

The following assays can be used to demonstrate the potency of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of adhesion where 100% = adhesion assessed in the absence of test compound and 0% = adhesion in the absence of cells or ICAM-1.

LFA-1-Dependent Cell Assay

96 well Nunc immunoplates were coated overnight with affinipure $F(ab)_2$ goat anti-human IgG Fc (Jackson ImmunoResearch) at 2 µg/ml in Dulbecco's phosphate-buffered saline (PBS). Plates were then blocked for Ih at RT with I% (w/v) bovine serum albumin (BSA) in PBS, and incubated with 200 ng/ml of 5-domain ICAM-1-human Fc construct in PBS for 2h. Inhibitors were serially diluted across plates in assay medium (RPMI 1640 + 10% foetal calf

serum), 3 × 10^5 HL60 cells added together with phorbol-12-myristate-13-aceteate (PMA) at 20 ng/ml in a total volume of 200µl. After 30 minutes incubation at 37°C, plates were washed twice in assay medium, adherent cells fixed in methanol and stained with 0.25% (w/v) Rose Bengal in PBS. After removal of unbound dye, bound dye was liberated with 100µl 1:1 PBS:ethanol and absorbance read at 570nm.

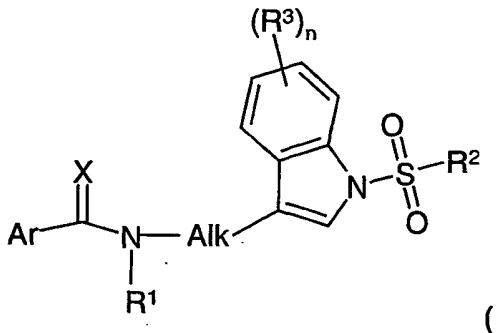
LFA-1-Dependent Protein-Protein Assay

96 well Nunc immunoplates were coated overnight with an anti-β2 integrin monoclonal antibody (KIM185) at 5 µg/ml in PBS. After blocking plates for 1h in PBS/2% BSA/1% Tween 20, 100µl of a lysate from HL60 cells in 20mM Tris/150mM NaCl/1mM $MnCl_2$/1% Nonidet P-40 was added for 3h at RT. After washing, wells received ICAM-1-human Fc (final concentration 2 µg/ml) in the presence of serial dilutions of inhibitors in conjugate buffer (20mM Tris/150mM NaCl/1mM $MnCl_2$/1% (w/v) ovalbumin) and plates were incubated for 2h at RT. After further washes, plates were incubated with a peroxidase-conjugated $F(ab)_2$ goat anti-human IgG Fc (Jackson ImmunoResearch) in conjugate buffer for 1 hour, washed finally, and the signal developed using TM Blue substrate with absorbance read at 630nm.

In the above cell assay compounds of the invention generally have IC_{50} values of 100µM and below. In the above protein assay compounds of the invention generally have IC_{50} values of 1µM and below.

CLAIMS

1. A compound of formula (1):



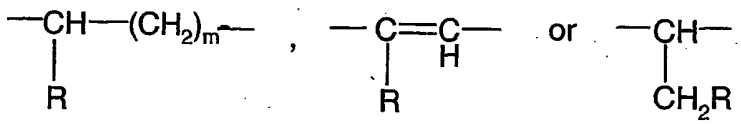
(1)

wherein:

Ar is an optionally substituted aromatic or heteroaromatic group;

X is an oxygen or sulphur atom;

Alk is a chain



in which m is zero or the integer 1or 2 and R is a carboxylic acid (-CO_2H) or a derivative or biostere thereof;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

R^2 is an optionally substituted aliphatic group;

R^3 is an atom or group $-L^1(Alk^1)_tL^2(R^4)_u$ in which L^1 and L^2 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^1 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^5$ [where R^5 is a hydrogen atom or an optionally substituted alkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-N(R^5)CO_2R^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $-N(R^5)CON(R^6)(R^7)$ [where R^7 is a

hydrogen atom or an optionally substituted alkyl group], -$N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^1 and L^2 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

n is zero or the integer 1, 2 or 3;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to claim 1 in which R^1 is a hydrogen atom.

3. A compound according to claim 1 or 2 in which Alk is a $-CH(R)CH_2-$ group.

4. A compound according to any one of claims 1 to 3 in which R is a carboxylic acid ($-CO_2H$) group.

5. A compound according to any one of claims 1 to 4 in which R^2 is an optionally substituted C_{1-6}alkyl group.

6. A compound according to any one of claims 1 to 5 in which Ar is an optionally substituted phenyl or pyridyl group.

7. A compound which is:

(2*S*)-2-[(3,5-dichloropyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;

(2*S*)-2-(2,6-dichlorobenzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;

(2*S*)-2-[(2-chloropyridine-3-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;

2-[2-chloro-4-(3-hydroxy-benzylcarbamoyl)-benzoylamino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;

2-(2,6-dichloro-benzoylamino)-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;

2-[(3,5-dichloro-pyridine-4-carbonyl)-amino]-3-(1-methanesulfonyl-1*H*-indol-3-yl)-propionic acid;
and the salts, solvates, hydrates and N-oxides thereof.

8. A pharmaceutical composition comprising a compound according to claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

9. Use of a compound according to any one of claims 1 to 7 for the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder in a mammal in which inappropriate leukocyte trafficking plays a role.

10. A use according to claim 9 wherein the disease or disorder is an acute or chronic inflammatory disease.

11. A use according to claim 9 wherein the disease or disorder is a inflammatory or hyperproliferative skin disease.

12. A use according to claim 11 wherein the inflammatory or hyperproliferative skin disease is selected from psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, eczematous dermatitis or seborrhoeic dermatitis.

13. Use of a compound according to any one of claims 1 to 7 for the manufacture of a medicament for inhibiting in a mammal the binding of LFA-1 to the ligands thereof.

14. A use according to claim 13 wherein the ligand is ICAM-1.

INTERNATIONAL SEARCH REPORT

PCT/GB 01/05050

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D209/20 A61K31/405

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 01 58853 A (HOFFMANN LA ROCHE) 16 August 2001 (2001-08-16) page 2, line 15-18; examples 215-222	1-14
P,A	WO 01 58893 A (MERCK PATENT GMBH ;GOODMAN SIMON (DE); GOTTSCHLICH RUDOLF (DE); WI) 16 August 2001 (2001-08-16) page 2, line 26; claim 1	1-14
A	WO 96 03430 A (OBERHAUSER BERNDT ;SANDOZ AG (AT); FOSTER CAROLYN ANN (AT); DREYFU) 8 February 1996 (1996-02-08) page 1, line 18 -page 2, line 8	1-14
A	WO 93 01169 A (MERCK SHARP & DOHME) 21 January 1993 (1993-01-21) page 20, line 33 -page 21, line 2; claims 2-4; examples 22,23	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2002	13/02/2002

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European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Von Daacke, A

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INTERNATIONAL SEARCH REPORT

PCT/GB 01/05050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0158853 A	16-08-2001	AU 3022701 A	20-08-2001
		WO 0158853 A1	16-08-2001
WO 0158893 A	16-08-2001	DE 10006139 A1	16-08-2001
		AU 3166401 A	20-08-2001
		WO 0158893 A2	16-08-2001
WO 9603430 A	08-02-1996	AT 187461 T	15-12-1999
		AU 702332 B2	18-02-1999
		AU 3222195 A	22-02-1996
		BR 9508342 A	21-10-1997
		CA 2192786 A1	08-02-1996
		CZ 9700221 A3	14-05-1997
		DE 69513837 D1	13-01-2000
		DE 69513837 T2	18-05-2000
		DK 775158 T3	22-05-2000
		WO 9603430 A1	08-02-1996
		EP 0775158 A1	28-05-1997
		ES 2142490 T3	16-04-2000
		FI 970279 A	23-01-1997
		GR 3032698 T3	30-06-2000
		HK 1014011 A1	08-09-2000
		HU 77388 A2	28-04-1998
		JP 10504540 T	06-05-1998
		NO 970340 A	27-01-1997
		NZ 291168 A	26-06-1998
		PL 317349 A1	01-04-1997
		PT 775158 T	31-05-2000
		SI 775158 T1	30-04-2000
		SK 11797 A3	09-07-1997
		US 6013627 A	11-01-2000
WO 9301169 A	21-01-1993	CA 2110514 A1	21-01-1993
		EP 0593559 A1	27-04-1994
		WO 9301169 A2	21-01-1993
		JP 6509087 T	13-10-1994
		US 5472978 A	05-12-1995
		AT 133657 T	15-02-1996
		AT 133658 T	15-02-1996
		AU 664188 B2	09-11-1995
		AU 2244092 A	11-02-1993
		CA 2110513 A1	21-01-1993
		CA 2110725 A1	21-01-1993
		DE 69208088 D1	14-03-1996
		DE 69208089 D1	14-03-1996
		EP 0522808 A2	13-01-1993
		EP 0593557 A1	27-04-1994
		EP 0593615 A1	27-04-1994
		WO 9301159 A1	21-01-1993
		WO 9301160 A1	21-01-1993
		WO 9301165 A2	21-01-1993
		IE 922185 A1	13-01-1993
		JP 6509332 T	20-10-1994
		JP 6509090 T	13-10-1994
		US 5610183 A	11-03-1997
		US 5629347 A	13-05-1997
		US 5495047 A	27-02-1996